A DIAGNOSTIC TEST FOR DISTINGUISHING PEMPHIGUS, DERMATITIS HERPETIFORMIS, DISSEMINATE LUPUS ERYTHEMATOSUS AND ERYTHEMA MULTIFORME EXUDATIVUM*

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The cataphoretic mobility-reducing action of the serums from patients with pemphigus, dermatitis herpetiformis, disseminate lupus erythematosus and erythema multiforme exudativum on the respective streptococci isolated from patients with each of these diseases, as shown by comparison with the mobility of these organisms in sodium chloride solution, was found to be so specific in experiments already recorded (1, 2, 3, 4) that an attempt was made to apply this action as a differential diagnostic test for these four diseases. The preliminary results of these studies have already been reported (5). This report deals with an analysis of the results of this test as applied to the serums of 322 patients.†

TECHNIC

Four antigens were used in this test. One consisted of a pool of strains of streptococci isolated from patients who had pemphigus, one consisted of a pool of strains isolated from patients who had dermatitis herpetiformis, one consisted of a pool of strains isolated from patients who had disseminate lupus erythematosus and another consisted of a pool of strains isolated from patients who had erythema multiforme exudativum. These streptococci were grown and stored as single strains in the manner already described for the handling of streptococci obtained from patients who had pemphigus, for the determination of cataphoretic mobility in immune serums (1). The strains which were to be included in the pool used as the pemphigus antigen and which were isolated from patients who had pemphigus were selected in the following manner. Each of these strains was tested individually against the serums obtained from each of five

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patients who had pemphigus and against control serums obtained from patients who had undisputed evidence of each of the other three diseases, by using the technic described in the study just referred to. Only those strains whose mobility was specifically reduced by the serum obtained from the patients who had undisputed pemphigus, and whose mobility was not reduced by control serums, were included in this pool. The strains which were included in the other three pools used as the dermatitis herpetiformis, lupus erythematosus and erythema multiforme antigens, were selected in each instance from the strains isolated in the same manner from patients who had one of these diseases. Each of these strains was tested with serums obtained from five patients who had the respective disease, and using appropriate control serums. The pooled antigens were diluted individually in triple distilled water, treated with formaldehyde, corked, shaken and stored in the refrigerator, by using the methods described in the investigations referred to previously.

The serums used for this study acted most specifically when the blood was drawn, after a night of fasting, into sterile, dry syringes; transferred to sterile, dry, chemically clean tubes, which were corked and stored in the refrigerator. Fat, hemolysis, contamination, autolysis, heat and chemicals rendered these serums unsatisfactory for testing. Some serums reduced equally and to a moderate degree the mobility of all of the streptococci used in the tests. This action was so marked with these serums as to render the test nondiagnostic. On inquiry it was found that most of these serums had been obtained from patients to whom large quantities of arsenic had been administered. This action might be attributable to the lowering of the surface tension of the globulin particles in the serum by the arsenic. Recent experiments have shown that inactivation of the serums (56°C. for twenty minutes), without altering the specific action, removed in many instances most of the nonspecific effect on the control antigens, which previously was manifested by serums drawn from patients who had an acute or toxic type of any of these four diseases. Inactivation was unnecessary in many serums, particularly those from patients who were suffering from the chronic form or a nontoxic phase of the disease, since under these conditions there was little nonspecific effect. In serums which were stored in the refrigerator for some weeks or months, much of the nonspecific effect disappeared. This observation is consistent with the findings of E. Rosenthal, in whose serologic studies fresh serums were found to possess a great deal of nonspecific effect. In Rosenthal's (6) experiments, aging of the serum destroyed, in most instances, the nonspecific action.

Each "set-up" consisted of four tubes, one containing 1 cc. of pooled pemphigus antigen, another containing 1 cc. of the dermatitis herpetiformis antigen, another containing 1 cc. of the lupus erythematosus antigen and the fourth containing 1 cc. of the erythema multiforme antigen. To each of these four suspensions was added 1 cc. of the serum to be tested, which was diluted 1:320 with freshly prepared, sterile 0.9 per cent solution of sodium chloride. This made the dilution 1:640 during incubation. If a negative test was obtained with all antigens at this dilution, the test was repeated, and the dilution of the serum was only a half that usually employed.

The tubes were thoroughly shaken. Each "set-up" was incubated fourteen minutes at 35°C., removed from the incubator, and 6 cc. of distilled water was immediately added to each tube. The procedure followed to determine the cataphoretic mobility of streptococci in each of these tubes has already been described (1). The presence in a serum of antibodies for one of the antigens was manifested by two phenomena: (1) the marked reduction of the mobility of the streptococci in the pool of strains of streptococci constituting that antigen, while the mobility of the streptococci in the other three pools was reduced equally and little more than it was shown to be reduced by normal serum; (2) a characteristic motion of the streptococci in the pool constituting that antigen, these streptococci moved steadily at a constant speed toward the anode and at the same time they seemed to roll or turn on themselves so that one surface after another was presented toward the anode. This motion was in marked contrast to that of the streptococci in the control pools. The latter moved in an even, sliding manner without a tendency to turn or roll. This striking characteristic motion of the streptococci which had been acted on by specific antibodies was easily distinguished from the "jerky" motion provoked by introduction of electrolytes into the system, in which circumstance the organisms seem to slide forward without turning on themselves, only to stop and rapidly jerk backward like a shuttle and then slide forward once more.

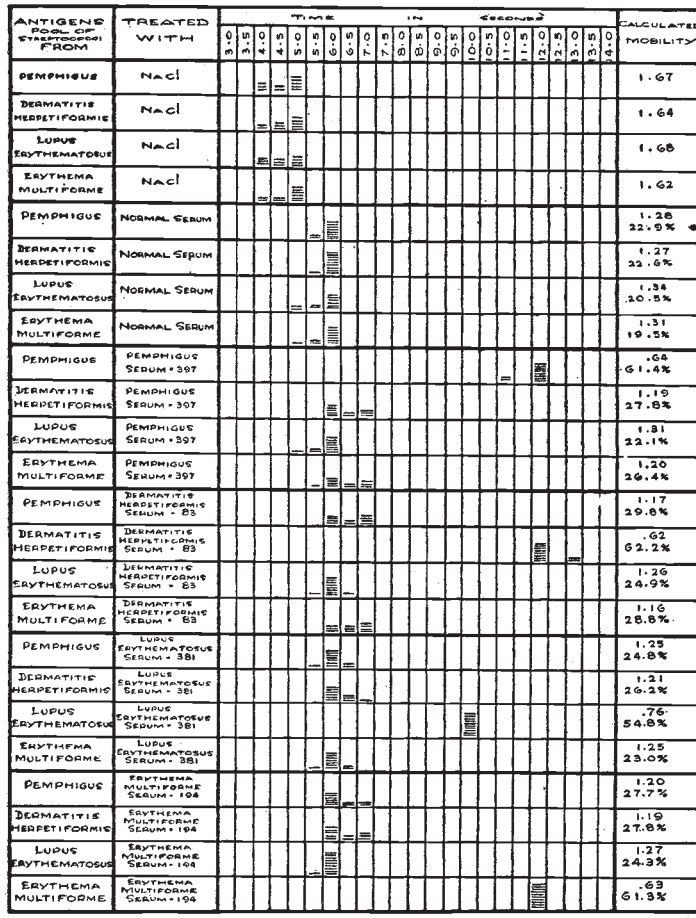
Figure 1 demonstrates the results of a typically positive test with the serum obtained from (1) one patient who had pemphigus, (2) one who had dermatitis herpetiformis, (3) one who had lupus erythematosus and (4) one who had erythema multiforme. It is to be noted that each serum reduced markedly the mobility of the streptococci in the pool of strains of streptococci isolated from patients who had the respective disease, whereas it reduced the mobility of the streptococci obtained from patients who had each of the other three diseases, little or no more than did normal serum. The average mobility of the streptococci in the pools varied slightly from day to day. Normal serum reduced slightly the mobility of all of the streptococci. The mobility of the nonspecific streptococci was reduced slightly more in the pathologic serums than in normal serum. This action is attributable to the presence of an increased amount of globulin (7) in the pathologic serums.

To date, 34,872 individual readings, comprising 2,234 tests with 462 serums obtained from 322 patients have been done. Two hundred and six of the patients had pemphigus, or dermatitis herpetiformis or disseminate lupus erythematosus or erythema multiforme exudativum, while 116 had either normal skins or were suffering from unrelated cutaneous or systemic diseases.

Analysis and consideration of the results of the test in cases of pemphigus

The tabulations in table 1 record the results of this test, together with the available clinical data, as it has been applied as a diagnostic test for pemphigus. Group A consists of the serums obtained in fifty-six cases in which the clinical diagnosis of pemphigus was undisputed. A positive test was obtained with the serum in each of these cases. In these fifty-six cases twenty-four patients died of pemphigus subsequent to the time blood was drawn for testing. At the time

of the last inquiry, the remaining thirty-two patients were alive and the disease was in various states of clinical remission, relapse or progression. As is indicated in this tabulation, positive tests were obtained with the serums of patients who were suffering from the following forms of the disease: acute and chronic types of pemphigus vulgaris, pemphigus vegetans, pemphigus foliaceus, Senear-



*Percentages represent the average reduction of mobility under the mobility in the salt solution control.

FIG. 1. Typical reactions obtained with serum in cases of pemphigus, dermatitis herpetiformis, lupus erythematosus and erythema multiforme.

Usher pemphigus, ocular pemphigus, and pemphigus that was limited to the mucous membranes. If a positive reaction with this serologic test could be considered a proof of the existence of this disease, several conclusions which are supported by clinical observations could be drawn. First, all of the mentioned clinical types are simply variations of the same disease process. Second, all patients who contract the disease do not die of it, but a few apparently recover (cases 106, 253, 287, 345). Third, pemphigus may begin with a syndrome which

TABLE 1

Results of the diagnostic test for pemphigus

CASE	DATE ON WHICH SERUM WAS RECEIVED	PHYSICIAN'S CLINICAL IMPRESSION WHEN BLOOD WAS DRAWN	SUBSEQUENT COURSE
Group A. Serums which were obtained in cases in which a definite clinical diagnosis of pemphigus was made, and which produced positive tests with the pemphigus antigen.			
60	3–26–34	Pemphigus vulgaris	Died of pemphigus, 9–24–34
107	2–12–34	Pemphigus vulgaris or erythema multiforme	Died of pemphigus 6 or 8 weeks after onset.
147	4–19–34	Pemphigus vulgaris	Died of pemphigus, May, 1934.
165	6–19–34	Pemphigus vulgaris	Died of typical pemphigus
173	6–26–34	Pemphigus vulgaris	Died of pemphigus one week later
181	7–26–34	Pemphigus vulgaris	Died of pemphigus, November, 1934
182	7–26–34	Pemphigus vulgaris	Died of pemphigus; biopsy typical of pemphigus; Pels' test toxic
199	8–8–34	Pemphigus vulgaris	Died of pemphigus, 8–11–34
202	8–8–34	Pemphigus vulgaris	Died of typical pemphigus, 10–14–34
203	8–13–34	Pemphigus vulgaris	Died in fall of 1934 of typical pemphigus; Pels' test 59 per cent—toxic
212	8–20–34	Pemphigus vulgaris	Died of pemphigus
214	8–20–34	Pemphigus vulgaris	Died of pemphigus, 9–6–34
227	9–4–34	Acute pemphigus vulgaris	Died of pemphigus, 2–3–35
233	8–19–34	Pemphigus vulgaris	Died of pemphigus 8 days later.
238	9–26–34	Pemphigus vulgaris	Died of pemphigus 3 weeks later.
250	11–17–34	Acute pemphigus vulgaris	Died of pemphigus, 11–27–35; Pels' test 70 per cent—toxic
257	12–17–34	Pemphigus vulgaris	Died of pemphigus, 3–5–35; 12–14–34, Pels' test 52 per cent—toxic, and 2–14–35, 54 per cent—toxic; positive with pemphigus antigen, 2–19–35.
298	3–27–35	Pemphigus vulgaris	Died of pemphigus
332	4–16–35	Bullous toxic erythema or pemphigus	Died of pemphigus, 6–4–35; Pels' test toxic, three specimens
366	7–24–35	Pemphigus vulgaris	Died of pemphigus, November, 1935.
373	8–2–35	Pemphigus vulgaris	Died of pemphigus
397	10–4–35	Pemphigus vulgaris	Died of pemphigus, 11–28–35; Pels' test toxic
432	10–29–35	Pemphigus vulgaris	Died one week later of pemphigus
435	11–19–35	Pemphigus vulgaris	Died of pemphigus, January, 1936.
38	4–28–33	Pemphigus vulgaris	4–4–36, lesions on body, scalp and neck; Pels' test 53 per cent
61	7–22–33	Pemphigus vulgaris	2–5–36, some free periods but usually lesions in eyes, mouth and vagina; Pels' test toxic
82	9–28–33	Pemphigus; ocular and oral	11–6–35, completely blind; lesions of eyes, mouth and throat; patient never had skin lesions
106	2–12–34	Pemphigus vulgaris	6–1–35, in remission; no mouth lesions past year; Pels' test toxic
108	2–15–34	Pemphigus foliaceous	6–15–35, patient in hospital; biopsy typical of pemphigus foliaceous

TABLE 1—*Continued*

CASE	DATE ON WHICH SERUM WAS RECEIVED	PHYSICIAN'S CLINICAL IMPRESSION WHEN BLOOD WAS DRAWN	SUBSEQUENT COURSE
		Group A—*Continued*	
110	2-15-34	Senear-Usher pemphigus	3-4-36, patient in hospital; clinical evidence of Senear-Usher pemphigus; 11-1-35, serum positive with pemphigus antigen.
128	2-28-34	Pemphigus vulgaris	3-19-34, in relapse; skin and mouth lesions; attack of foliaceous type, 1931; vulgaris type, September, 1935
131	3-13-34	Pemphigus vulgaris	Lost contact with patient. Was clinically typical pemphigus vulgaris
154	5-7-34	Pemphigus vulgaris	7-16-35, mucous membranes clear; axillary lesions healing; clinically pemphigus vegetans.
156	5-14-34	Pemphigus vulgaris	7-3-35, clinically pemphigus
163	6-2-34	Pemphigus or dermatitis herpetiformis	4-1-36, under treatment; new lesions regularly; had stormy course; clinically pemphigus.
167	6-21-34	Pemphigus foliaceous	3-31-35, some skin lesions; clinically pemphigus foliaceous
169	6-22-34	Chronic pemphigus	6-7-35, improved; diagnosed pemphigus by several dermatologists
180	7-19-34	Senear-Usher pemphigus	Last seen October, 1934; then severe pemphigus; diagnosed pemphigus by several dermatologists.
200	8-9-34	Pemphigus vulgaris	3-18-36, in hospital; very weak; generalized eruption.
204	8-8-34	Pemphigus of conjunctiva	8-7-35, condition unchanged
245	11-3-34	Pemphigus foliaceous or arsenical dermatitis	3-28-36, in hospital; clinically pemphigus
247	11-13-34	Pemphigus vulgaris	4-1-36, improved; April, 1934, clinically Senear-Usher pemphigus; later, pemphigus vulgaris; Pels' test 55 per cent—toxic. Nikolsky's sign positive.
253	12-3-34	Senear-Usher pemphigus	4-14-36, in remission; 12-3-34, clinically Senear-Usher pemphigus
281	2-18-35	Pemphigus vulgaris	5-6-36, confined to bed; typical severe pemphigus
287	3-5-35	Oral pemphigus	November, 1935, in remission; 3-5-35, clinically classic pemphigus
297	3-27-35	Ocular and nasal pemphigus	3-2-36, eye lesions progressive; nose improved; Pels' test toxic
344	4-1-36	Pemphigus vulgaris	3-30-36, in remission; treated by Davis' method and mocassin venom; Pels' test toxic; 5-20-35, serum positive only with dermatitis herpetiformis antigen.
345	5-17-35	Pemphigus vulgaris	3-24-35, in remission; given Germanin and had dental extractions; 3-20-36, negative serum with pemphigus antigen

TABLE 1—*Continued*

CASE	DATE ON WHICH SERUM WAS RECEIVED	PHYSICIAN'S CLINICAL IMPRESSION WHEN BLOOD WAS DRAWN	SUBSEQUENT COURSE
		Group A—*Continued*	
389	8–2–35	Pemphigus foliaceous	2–28–36, in hospital; failing; diagnosed pemphigus foliaceous at Minnesota Dermatological Society, spring of 1935; diagnosed dermatitis herpetiformis at University of Minnesota, 1927
400	3–23–36	Pemphigus vegetans or erythema multiforme	3–28–36, typical pemphigus vegetans; 10–4–35, serum positive only with erythema multiforme antigen, then clinically pemphigus or erythema multiforme; Pels' test toxic; 5–18–36, serum positive with pemphigus antigen
403	10–14–35	Pemphigus vulgaris	5–12–36, in partial remission; began in mouth after dental extraction; skin lesions six months later.
404	10–15–35	Oral pemphigus	3–19–36, typical pemphigus, bullae in mouth and pharynx; serum again reacted positive with pemphigus antigen
442	12–9–35	Senear-Usher pemphigus	4–19–36, unchanged; Pels' test toxic; diagnosis pemphigus by several dermatologists
465	4–3–36	None given	4–14–36, typical pemphigus foliaceous
471	4–24–36	Pemphigus vulgaris	Hospitalized; typical pemphigus vulgaris
485	5–4–36	Pemphigus vulgaris	Hospitalized; typical pemphigus vulgaris
		Group B. Serums which were obtained in cases in which a definite clinical diagnosis of pemphigus was made, and which produced negative tests with the pemphigus antigen.	
149	4–29–34	Pemphigus foliaceous	7–19–34, died; no necropsy; probable diagnosis, pemphigus; biopsy not typical
222	8–25–34	Acute pemphigus, erythema multiforme or dermatitis medicamentosa	Blood drawn fifth day of illness; patient died on ninth day; necropsy—cloudy swelling of parenchymatous organs, bronchopneumonia, septic pulmonary infarcts—the picture of intense toxemia. Diagnosis, acute pemphigus.
		Group C. Serums which were obtained in cases in which a clinical diagnosis of pemphigus has not been established definitely, and which produced positive tests with pemphigus antigen.	
75	9–13–33	Pemphigus or dermatitis herpetiformis	Observed at clinic eight months; clinically pemphigus or dermatitis herpetiformis; situation of lesions favored pemphigus; no pruritus, occasional bullae in mouth and nose up to April, 1936. Four specimens of blood positive with pemphigus antigen.

TABLE 1—*Continued*

CASE	DATE ON WHICH SERUM WAS RECEIVED	PHYSICIAN'S CLINICAL IMPRESSION WHEN BLOOD WAS DRAWN	SUBSEQUENT COURSE
		Group C—*Continued*	
139	4–12–34	Pemphigus or erythema multiforme	11–19–35, in remission; dental foci removed; occasional lesions first year.
144	5–2–34	Pemphigus or dermatitis herpetiformis	3–4–36, clinically dermatitis herpetiformis or pemphigus; presented in 1928, Chicago Dermatological Society, with full blown pemphigus; numerous Pels' tests toxic or borderline
177	7–5–34	Pemphigus vulgaris	Lost
184	7–24–34	Pemphigus vulgaris	2–29–36, partial remission; occasional bullae in umbilicus; 4–21–36, serum positive with pemphigus antigen, diagnosed pemphigus by four dermatologists during attacks.
193	7–26–34	Acute septic pemphigus	5–7–36, bedridden most of time, febrile; status of skin unknown; Pels' test 54 per cent—toxic
243	10–26–34	Acute septic pemphigus	3–5–36, in remission since Nov. 1935; 10–26–34, profound toxemia, clinically severe pemphigus.
246	11–15–34	Ocular pemphigus	3–6–36, eye involvement stationary; no skin lesions
295	3–20–35	Pemphigus or erythema multiforme	3–19–35, clinically erythema multiforme or pemphigus; 3–22–35, toxic, clinically pemphigus; stormy course; left hospital in poor condition with generalized eruption; Pels' test 67 per cent; March, 1936, alive; status of skin unknown
349	6–4–35	Vernal conjunctivitis and aphthous stomatitis, or ocular and oral pemphigus	October, 1935, slightly improved diagnosis at home, ocular and oral pemphigus; March, 1936, improved; lesions persist
374	8–8–35	Dermatitis herpetiformis or pemphigus or bullous pyoderma	3–28–36, clinically pemphigus or bullous pyogenic eruption
463	2–22–36	None given	3–24–36, mouth lesions characteristic of pemphigus; skin lesions nondescript.
		Group D. Serums which were obtained in cases in which the probable clinical diagnosis was pemphigus, but which produced negative tests with pemphigus antigen and positive tests with other antigens.	
123	2–21–34	Pemphigus vulgaris (benign)*	Lost; last seen 7–13–34; clinically unchanged. Pels' test 67 per cent
124	2–21–34	Possible pemphigus*	December, 1935, only one attack; cured with viosterol; health good. October, 1933, diagnosed pemphigus at Minnesota Dermatological Society.

* Antigen producing positive test: Dermatitis herpetiformis.

TABLE 1—*Continued*

CASE	DATE ON WHICH SERUM WAS RECEIVED	PHYSICIAN'S CLINICAL IMPRESSION WHEN BLOOD WAS DRAWN	SUBSEQUENT COURSE
		Group D—*Continued*	
236	9–27–34	Pemphigus*	6–5–35, clear; recurrent fall attacks three years; lesions only on dorsum of hands and one eyelid; cleared on intravenous injection of mercurochrome 220; Pels' test 60 per cent
264	1–4–35	Dermatitis herpetiformis pemphigus or erythema multiforme*	3–28–36, died of bronchopneumonia; diagnosed pemphigus by some and dermatitis herpetiformis by others. Two earlier serums obtained by another doctor were positive with dermatitis herpetiformis antigen
183	7–23–34	Senear-Usher syndrome†	4–2–36, died; positive blood culture for hemolytic streptococci antemortem; necropsy—septicemia, chronic fibrous pleuritis, fatty vacuolization of liver, pyelonephritis; skin clinically pemphigus
Group E. Serums which were obtained in cases in which the clinical diagnosis was not pemphigus, but which produced positive test with pemphigus antigen.			
155	5–11–34	Pemphigus vulgaris	Last seen fall of 1934; dermatitis herpetiformis favored; 5–11–34, generalized bullous eruption and mouth lesions; positive Nikolsky's sign; pemphigus favored; 10–29–34, serum positive with pemphigus antigen; died of pneumonia; no autopsy; skin lesions present
170	6–23–34	None given	3–4–36, eruption persists; incapacitated; last seen June, 1934; dermatitis herpetiformis favored.
176	7–4–34	Pemphigus vulgaris or dermatitis herpetiformis	Last seen fall, 1934, dermatitis herpetiformis favored; lesions skin two years; mouth five years. Diagnosed pemphigus by another dermatologist.
427	10–20–35	Pemphigus?	3–4–36, diagnosed Vincent's angina; alive, April, 1936, lesions cleared; 10–20–35, had ulceration of gums, buccal mucosa and hard palate (two years); recently spread downward, weakness, fever, blebs in pharynx; 5–11–36, serum positive with pemphigus antigen.

† Antigen producing positive test: Lupus erythematosus.

TABLE 1—*Concluded*

CASE	DATE ON WHICH SERUM WAS RECEIVED	PHYSICIAN'S CLINICAL IMPRESSION WHEN BLOOD WAS DRAWN	SUBSEQUENT DIAGNOSIS
Group F. Serums which were obtained in cases in which a tentative clinical diagnosis of pemphigus was entertained, but which produced negative tests with the pemphigus antigen.			
105			Bullous impetigo
146			Dermatitis medicamentosa
150			Dermatitis medicamentosa (amytal)
142			Idiopathic exfoliating dermatitis
160			Ulcer of the foot (etiology undetermined)
187			Sprue
206			Lymphatic leukemia
213			Dermatitis medicamentosa (phenolphthalein)
278			Submucous thrush
296			Malignant erythroderma
428			Dermatitis venenata with generalized exfoliation
431			Recurrent vesicular eruption of mouth and glans penis (etiology undetermined); 3–4–36, well.
444			Beriberi
455			Aphthous stomatitis.

Group G. Serums obtained from patients who had diseases distinct from pemphigus and from normal persons whose serums produced negative tests with pemphigus antigen.

Herpes zoster	9	Cold allergy	1	Ulcers of mouth (food sensitivity)	1
Recurrent herpes	4	Erythema nodosum	1	Aphthous stomatitis	1
Pityriasis rosea	5	Eczema of hands	1	Normal persons	8
Herpes facialis	2	Contact dermatitis	2	Rosacea-like tuberculid of Lewandowsky	1
Discoid lupus erythematosus	9	Scleroderma	4	Erythema multiforme	34
Dermatitis mediamentosa	6	Neurodermatitis	1	Disseminate lupus erythematosus (two recovered)	22
Lichen planus	4	Hodgkin's disease	1	Dermatitis herpetiformis	55
Infantile eczema	3	Summer prurigo	1	Herpes gestationes	5
Infectious eczematoid dermatitis	3	Sarcoid	1	Cases in which clinical diagnosis was not yet definitely established, all of which were suspected dermatitis herpetiformis	11
Pyoderma gangrenosum	1	Acne rosacea	2		
Pellagra	2	Toxic erythema (etiology undetermined)	1		
Angioneurotic edema	1	Trichophytosis and trichophytid (bullous)	3		
Atopic eczema	17				
Varicella	4				
Urticaria	2				

clincially and serologically is either dermatitis herpetiformis (case 344) or erythema multiforme (case 400). Case 389 is also interesting from this standpoint.

In one case in which opportunity afforded (case 345) a test performed with serum drawn long after clinical remission was negative, while during the attack a positive test was obtained. This would seem to indicate that the patient had completely recovered and, as in the case in other streptococcal diseases, the antibodies gradually had disappeared from the blood. A positive test obtained with serum drawn during a clinical remission might be interpreted as evidence of the production of antibodies due to the continued presence of the organism on the mucous surfaces or in foci of infection. Relapses might be expected in such cases.

Group B consists of the serums obtained in two cases in which a definite clinical diagnosis of pemphigus was made, but in which negative tests were obtained with the pemphigus and control antigens. In case 149 all antigens had their mobility reduced considerably more by this serum than by normal serum. The effect was equal on each antigen. This effect on nonspecific antigens has been seen with the serums obtained from patients who had been given large quantities of arsenic before the blood was drawn for testing. A possible explanation of this action already has been given. Determination has not been made regarding administration of arsenic to the patient in this case. In regard to case 222, the question of classification arises. Acute septic pemphigus of the type that follows septic wounds or acute febrile diseases such as scarlet fever and measles, or of the type that follows the handling of animal products or that occurs after vaccination, occupies a doubtful position in the classification of true pemphigus. Many authors believe acute pemphigus is distinct from the acute form of pemphigus vulgaris and that it is essentially a septicemic process caused by any one of several organisms varying in type from the hemolytic streptococci to Escherichia coli. The literature on this subject has been reviewed thoroughly by E. Riecke (8). If the patient representing case 222 had simply the acute form of pemphigus vulgaris, then the failure of the test to demonstrate antibodies in the blood may be explained by the fact that the blood used for testing was drawn on the fifth day of an illness which caused death in nine days after its onset, and it would seem reasonable that if any antibodies had been formed in this short period during such an overwhelming infection, they were formed in such a small quantity that they were not detectable by this method.

Group C consists of the serums obtained in twelve cases in which a clinical diagnosis of pemphigus has not been established definitely. A positive test was obtained, with the serum obtained in each of these cases. Contact with one of these patients (case 177) has been lost. In cases 75, 139, 177, 184, 193, 243, 246, 295 and 463 (nine of the twelve) the clinical findings were those of pemphigus at the time blood was drawn for testing. In none of these cases has pemphigus been unquestionably ruled out clinically. Further observation of some of these patients may settle the question of diagnosis. In those patients in which a remission is present the diagnosis by clinical means cannot be definitely estab-

lished if the remission continues. Repeated serologic studies will be made in these cases.

In group D are included the serums obtained in five cases in which a clinical diagnosis of pemphigus was favored but in which the serums produced negative tests with the pemphigus antigen, and the tests with one of the control antigens were positive. In four cases the tests with the dermatitis herpetiformis antigen were positive and in the fifth case the test with the lupus erythematosus antigen was positive. In case 103 the question of a pemphigoid type of lupus erythematosus was raised.

Group E consists of the serums obtained in four cases in which a clinical diagnosis of pemphigus was not made but in which the blood serum gave a positive test with the pemphigus antigen. In cases 155, 170 and 176 a clinical diagnosis of dermatitis herpetiformis was favored. In case 427 a clinical diagnosis of Vincent's angina was made. In this case blood serum which was drawn May 11, 1936 gave a positive test with the pemphigus antigen. The positive test obtained during clincial remission suggested that the patient is still harboring the organism, as antibodies were still demonstrable in her blood. Further study of cases 170, 176, and 427 is desirable. It will be noted from analysis of groups C, D, and E that when clinical diagnosis and laboratory diagnosis disagreed the question of differentiation of pemphigus and dermatitis herpetiformis was chiefly concerned. This is in accord with the difficulty encountered at times in distinguishing clinically between these two dermatoses.

Group F includes the serums obtained in fourteen cases in which a tentative clinical diagnosis of pemphigus was entertained but in which it eventually was shown that the patients were suffering from disease totally unrelated to pemphigus. All of these serums gave negative tests with the pemphigus antigen.

Group G consists of a control group of serums obtained from 229 patients who had cutaneous or systemic diseases that were definitely distinct from pemphigus, or who were well persons. Negative test with the pemphigus antigen was obtained with each serum.

It is apparent that positive tests with the pemphigus antigen were obtained with the serums obtained in seventy-two cases. In fifty-six of the cases (group A) an undisputed clinical diagnosis of pemphigus was made, in twelve cases (group C) a probable, but as yet not definitely established clinical diagnosis of pemphigus was made, and in four cases (group E) a clinical diagnosis other than pemphigus was made. Negative tests with the pemphigus antigen were obtained with the serums drawn from 250 cases. In two cases (group B) a definite clinical diagnosis of pemphigus was made but negative tests were obtained with all antigens. In five cases (group D) a clinical diagnosis of pemphigus was favored, but in four of these cases a positive test was obtained with the dermatitis herpetiformis antigen and in the fifth case a positive test was obtained with the lupus erythematosus antigen. In fourteen cases (group F) pemphigus was suspected on clinical grounds but in each instance it was later ruled out. In 229 cases (group G) the clinical diagnosis was definitely not pemphigus, but various other cutaneous and systemic diseases were present.

Analysis and consideration of the results of the test in cases of dermatitis herpetiformis

Table 2 shows the results of this test and the available clinical data in cases of dermatitis herpetiformis. Group A consists of the serums obtained in fifty-five cases in which the clinical diagnosis of dermatitis herpetiformis was definite. A positive test was obtained with the dermatitis herpetiformis antigen in each of these serums. In one instance (case 265) a serum drawn early in the course of the disease produced a positive test with the erythema multiforme antigen and a negative reaction with the dermatitis herpetiformis antigen and serum drawn later in the course of the disease produced a positive test with the dermatitis herpetiformis antigen and a trace of reaction with the erythema multiforme antigen. This raises the question whether or not the dermatitis at first may begin as what is clinically and serologically erythema multiforme only to change later to dermatitis herpetiformis. Considering the similarity of the respective streptococci isolated from patients who have either of these two diseases, such a possibility does not seem improbable.

Group B includes the serums obtained in five cases in which the clinical diagnosis was herpes gestationes. Each of these serums produced a positive test with the dermatitis herpetiformis antigen. This would seem to indicate that these two dermatoses are identical in genesis. This impression is held by many observers (9).

Group C includes the serums obtained in twelve cases in which the clinical diagnosis of dermatitis herpetiformis has not been definitely established. Each of these serums produced a positive test with the dermatitis herpetiformis antigen. Contact with two of these patients (cases 336 and 234) has been lost. In none of these cases has dermatitis herpetiformis been unquestionably ruled out clinically. In most instances, clinical diagnosis of dermatitis herpetiformis was favored at the time of the last follow-up. Analysis of the facts recorded in the last column of the table shows that the differentiation clinically of dermatitis herpetiformis and pemphigus most often was concerned. Further observation of these patients may settle the diagnosis definitely.

Group D consists of the serums obtained in three cases in which a clinical diagnosis of dermatitis herpetiformis was favored, but in which the serum produced a positive test with one of the control antigens, which in each instance was the pemphigus antigen. Each of these patients was observed for only a short time. One (case 155) died of pneumonia; no necropsy was performed. The other two cases need further study. Again, the question of clinical differentiation of dermatitis herpetiformis and pemphigus is concerned.

Group E consists of the serums obtained in three cases in which a clinical diagnosis of dermatitis herpetiformis was not made, but in which the serums produced a positive test with the dermatitis herpetiformis antigen. In each instance the clinical impression favored the diagnosis of pemphigus. Contact with one of these patients (case 123) has been lost. The subsequent course of the other two is recorded. It is interesting that each patient had only one attack and that complete recovery ensued.

Group F includes the serums obtained in six cases in which a tentative clinical

TABLE 2

Results of the diagnostic test for dermatitis herpetiformis

CASE	DATE ON WHICH SERUM WAS RECEIVED	PHYSICIAN'S CLINICAL IMPRESSION WHEN BLOOD WAS DRAWN	SUBSEQUENT COURSE
Group A. Serums which were obtained from cases in which a definite clinical diagnosis of dermatitis herpetiformis was made, and which produced positive tests with dermatitis herpetiformis antigen.			
7	1–27–33	Dermatitis herpetiformis	4–17–36, clinically dermatitis herpetiformis; serum again positive with dermatitis herpetiformis antigen; positive to potassium iodide by mouth and by patch.
21	3–14–33	Dermatitis herpetiformis	8–12–34, eruption still present; positive to potassium iodide by patch and by mouth; duration four years.
80	9–26–33	Dermatitis herpetiformis	3–10–36, clinically dermatitis herpetiformis; positive patch to potassium iodide.
81	9–28–33	Dermatitis herpetiformis	7–18–34, in acute flare-up of dermatitis herpetiformis; positive patch to potassium iodide.
83	9–28–33	Dermatitis herpetiformis	2–7–36, clinically dermatitis herpetiformis; serum again positive with dermatitis herpetiformis antigen; positive patch to potassium iodide.
109	2–12–34	Dermatitis herpetiformis	6–28–35, clinically dermatitis herpetiformis.
112	2–14–34	Dermatitis herpetiformis	6–5–35, having cyclic recurrences of dermatitis herpetiformis.
113	2–15–34	Dermatitis herpetiformis	6–5–35, clinically dermatitis herpetiformis; began in mouth; 7–30–34, serum positive with dermatitis herpetiformis antigen.
119	2–19–34	Dermatitis herpetiformis	6–3–35, clinically dermatitis herpetiformis; now twenty-one years old, began at six.
136	4–6–34	Dermatitis herpetiformis	12–3–34, clinically dermatitis herpetiformis; positive patches to potassium iodide and potassium bromide.
151	4–30–34	Dermatitis herpetiformis	6–5–35, typical dermatitis herpetiformis; twenty-five years' duration.
153	5–7–34	Dermatitis herpetiformis	6–3–35, clinically dermatitis herpetiformis.
164	6–11–34	Dermatitis herpetiformis	4–28–35, dermatitis herpetiformis still present; 8–19–35, serum positive with dermatitis herpetiformis antigen.
171	7–5–34	Dermatitis herpetiformis	7–19–35, clinically dermatitis herpetiformis.

TABLE 2—*Continued*

CASE	DATE ON WHICH SERUM WAS RECEIVED	PHYSICIAN'S CLINICAL IMPRESSION WHEN BLOOD WAS DRAWN	SUBSEQUENT COURSE
		Group A—*Continued*	
174	7–26–34	None given	2–29–36, clinically dermatitis herpetiformis.
178	7–12–34	Dermatitis herpetiformis	7–31–35, dermatitis herpetiformis present; positive patch to potassium iodide.
186	7–25–34	Dermatitis herpetiformis	7–25–34, clinically dermatitis herpetiformis; Lost.
189	7–27–34	Dermatitis herpetiformis	2–9–36, dermatitis herpetiformis present; positive patch to potassium iodide.
195	7–31–34	Dermatitis herpetiformis	6–5–35, typical course dermatitis herpetiformis; duration eight years; died of pneumonia, January, 1935.
196	8–1–34	Dermatitis herpetiformis	12–7–34, dermatitis herpetiformis still present.
201	8–8–34	Dermatitis herpetiformis	10–25–35, clinically dermatitis herpetiformis when last seen.
215	8–23–34	Dermatitis herpetiformis	5–4–35, cyclic recurrences dermatitis herpetiformis; positive patch to potassium iodide; duration six years.
216	8–21–34	Dermatitis herpetiformis	10–22–35, clinically dermatitis herpetiformis when last seen.
217	8–21–34	Dermatitis herpetiformis	10–15–35, clinically dermatitis herpetiformis; duration nine years.
218	8–21–34	Dermatitis herpetiformis	10–15–35, clinically dermatitis herpetiformis.
219	8–21–34	Dermatitis herpetiformis	10–25–35, clinically dermatitis herpetiformis, when last seen; attacks for twenty years.
220	8–21–34	Dermatitis herpetiformis	10–15–35, typical dermatitis herpetiformis
221	8–21–34	Dermatitis herpetiformis	10–25–35, clinically dermatitis herpetformis when last seen.
223	8–29–34	Dermatitis herpetiformis	3–5–35, in flare of dermatitis herpetiformis
231	9–15–34	Pemphigus or dermatitis herpetiformis	3–4–36, typical dermatitis herpetiformis. Died, 1935, of pneumonia
232	9–17–34	None given	3–24–36, typical dermatitis herpetiformis. Serum again positive with antigen
242	10–19–34	Dermatitis herpetiformis	5–21–35, cyclic flares of dermatitis herpetiformis
265	4–16–36	Erythema multiforme	3–28–36, dermatitis herpetiformis; cyclic flares; 1–10–35, serum positive only with erythema multiforme antigen.

TABLE 2—*Continued*

CASE	DATE ON WHICH SERUM WAS RECEIVED	PHYSICIAN'S CLINICAL IMPRESSION WHEN BLOOD WAS DRAWN	SUBSEQUENT COURSE
		Group A—*Continued*	
266	1–10–35	Dermatitis herpetiformis	3–28–36, typical dermatitis herpetiformis; positive patch to potassium iodide
269	1–16–35	Dermatitis herpetiformis	3–4–36, typical dermatitis herpetiformis
275	2–1–35	Dermatitis herpetiformis	8–5–35, typical dermatitis herpetiformis
343	5–8–35	Dermatitis herpetiformis	Lost; typical dermatitis herpetiformis; 5–8–35, positive patches to potassium iodide and potassium bromide
356	6–26–35	Dermatitis herpetiformis	9–26–35, typical dermatitis herpetiformis; positive patch to potassium iodide
363	7–15–35	Dermatitis herpetiformis	5–28–36, typical dermatitis herpetiformis; flare from potassium iodide by mouth; lesions of mouth and vulva; 2–26–36, serum positive with dermatitis herpetiformis antigen
364	7–15–35	Dermatitis herpetiformis	7–15–35, clinically dermatitis herpetiformis; lost; positive patch to potassium iodide
390	9–6–35	Dermatitis herpetiformis	3–4–36, clinically dermatitis herpetiformis; positive patches to potassium iodide and potassium bromide
392	9–15–35	Dermatitis herpetiformis	2–17–36, cyclic flares of dermatitis herpetiformis; negative patch to potassium iodide and potassium bromide; flared by potassium bromide by mouth.
396	9–26–35	Dermatitis herpetiformis	9–26–35, clinically dermatitis herpetiformis; lost; positive patches to potassium iodide and potassium bromide.
429	10–21–35	Possibly pemphigus	3–9–36, dermatitis herpetiformis; 11–15–35, serum positive with dermatitis herpetiformis antigen.
434	11–11–35	Dermatitis herpetiformis	4–10–36, typical dermatitis herpetiformis; positive patch to potassium iodide
445	12–20–35	Dermatitis herpetiformis	3–9–36, typical dermatitis herpetiformis positive patches to potassium iodide and potassium bromide; flare from potassium iodide orally.
448	1–8–36	Dermatitis herpetiformis	1–8–36, typical dermatitis herpetiformis; lost; positive patch to potassium iodide.

TABLE 2—*Continued*

CASE	DATE ON WHICH SERUM WAS RECEIVED	PHYSICIAN'S CLINICAL IMPRESSION WHEN BLOOD WAS DRAWN	SUBSEQUENT COURSE
		Group A—*Continued*	
456	3–10–36	Dermatitis herpetiformis or erythema multiforme	5–13–36, typical dermatitis herpetiformis; positive patch to potassium iodide.
457	3–16–36	None given	3–24–36, clinically dermatitis herpetiformis
460	3–18–36	Dermatitis herpetiformis	3–18–36, clinically dermatitis herpetiformis; Lost
462	3–20–36	Dermatitis herpetiformis	3–20–36, typical dermatitis herpetiformis; twenty years' duration; positive patch to potassium iodide.
468	4–15–36	Dermatitis herpetiformis	Now at clinic; typical dermatitis herpetiformis
473	4–27–36	None given	5–12–36, typical dermatitis herpetiformis.
486	5–5–36	Dermatitis herpetiformis or dermatitis medicamentosa	Typical dermatitis herpetiformis; flared by potassium iodide by mouth; diagnosed pemphigus one and a half years ago by home doctor
331	4–1–35	Dermatitis herpetiformis or erythema multiforme	Flared, June, 1935. On 9–15–35 clinically dermatitis herpetiformis; positive patch to potassium iodide; responded to arsenic
		Group B. Serums which were obtained in cases in which the clinical diagnosis was herpes gestationes, and which produced positive tests with dermatitis herpetiformis antigen.	
125*	2–23–34	Herpes gestationes	6–3–35, clinically herpes gestationes; cleared after delivery
152	5–6–34	Herpes gestationes	June, 1935, cleared following delivery; no recurrence; typical herpes gestationes
240*	10–9–34	Herpes gestationes or pemphigus	3–3–36, well since December, 1934; vesicular eruption grouped like dermatitis herpetiformis; positive Nikolsky's sign; few mouth lesions three weeks before she had a miscarriage at the eighth month; stormy course; Pels' test 65 per cent.
262	12–31–34	Herpes gestationes	5–7–36, clinically herpes gestationes
386	8–26–35	Herpes gestationes	2–28–36, clinically dermatitis herpetiformis; persisted two months after delivery; one recurrence.

* Serum diluted 1:320 instead of using dilution of 1:640.

TABLE 2—*Continued*

CASE	DATE ON WHICH SERUM WAS RECEIVED	PHYSICIAN'S CLINICAL IMPRESSION WHEN BLOOD WAS DRAWN	SUBSEQUENT COURSE
Group C. Serums which were obtained in cases in which a clinical diagnosis of dermatitis herpetiformis has not been definitely established, but which produced positive tests with dermatitis herpetiformis antigen.			
235	9–24–34	Dermatitis herpetiformis or erythema multiforme	Seen daily two years; recurrent urticarial, erythematous lesions on elbows; pruritus; positive to potassium iodide by patch and by mouth, with vesicles; 2–13–36, serum positive with dermatitis herpetiformis antigen.
264	1–4–35	Dermatitis herpetiformis, pemphigus or erythema multiforme	Two earlier specimens from another source gave positive tests with dermatitis herpetiformis antigen; patient died of bronchopneumonia; diagnosis, pemphigus or dermatitis herpetiformis
271	1–12–35	Dermatitis herpetiformis or pemphigus	2–20–36, well; clinically dermatitis herpetiformis "with possibility of eventuating in pemphigus"
336	4–22–35	Dermatitis herpetiformis; features of pemphigus	Lost; 4–22–35, duration forty years; grouped vesicles; sharp burning; eosinophilia; good health; negative patch to potassium iodide; positive Nikolsky's sign
368	7–26–35	Dermatitis herpetiformis, pemphigus or erythema multiforme	5–6–36, clinically dermatitis herpetiformis; 7–26–36, dermatitis herpetiformis or pemphigus, cleared; relapsed; pruritus
447	1–8–36	Pemphigus foliaceous	5–1–36, cleared once; relapsed; now improved; a typical dermatitis herpetiformis
118	2–17–34	Probably dermatitis herpetiformis. Pemphigus?	6–5–35, clinically dermatitis herpetiformis; negative Nikolsky's sign five years' duration
166	6–22–34	Pemphigus; bullous iododerma; bullous erythema multiforme	3–28–36, clinically dermatitis herpetiformis; possibility of chronic eczema; itching eruption in patches; no bullous lesions since first acute outbreak
229	9–10–34	None given	4–24–36, well; skin clear; dermatitis herpetiformis or pemphigus; 9–10–34, cleared; recurred in 1935.
234	9–19–34	Dermatitis herpetiformis or pemphigus	Lost; dermatitis herpetiformis favored clinically 9–19–34
248	11–16–34	Pemphigus or dermatitis herpetiformis	4–1–36, in recurrence; grouping of dermatitis herpetiformis; crops of lesions; pruritus; good physically; had mouth lesions.

TABLE 2—*Continued*

CASE	DATE ON WHICH SERUM WAS RECEIVED	PHYSICIAN'S CLINICAL IMPRESSION WHEN BLOOD WAS DRAWN	SUBSEQUENT COURSE
		Group C—*Continued*	
360	4–19–36	Bullous lupus erythematosus?	4–7–36, dermatitis herpetiformis favored; diagnosis not definitely established; 7–5–35, serum negative with dermatitis herpetiformis antigen.

Group D. Serums which were obtained in cases in which the clinical diagnosis was dermatitis herpetiformis, but which produced negative tests with dermatitis herpetiformis antigen and positive tests with other antigens.

170	6–23–34	None given	3–4–36, eruption persists; last seen June, 1934; then dermatitis herpetiformis favored; biopsy favored dermatitis herptiformis
176	7–4–34	Pemphigus vulgaris	Last seen fall of 1934 when dermatitis herpetiformis was favored; lesions of skin two years and mouth five years; diagnosed pemphigus by another dermatologist. 8–13–34, serum positive with pemphigus antigen; alive April, 1936.
155	5–11–34	Pemphigus vulgaris	Last seen fall of 1934, dermatitis herpetiformis favored; 5–11–34, generalized bullous eruption with mouth lesions; positive Nikolsky's sign; pemphigus favored; 10–29–34, serum positive with pemphigus antigen; recently died of pneumonia; no necropsy.

Group E. Serums which were obtained in cases in which the clinical diagnosis was not dermatitis herpetiformis, but which produced positive tests with dermatitis herpetiformis antigen.

123	2–21–34	Pemphigus (benign)	Lost; 7–13–34, unchanged; Pels' test 67 per cent
124	2–21–34	Pemphigus?	December, 1935, cleared on viosterol; health good
236	9–27–34	Pemphigus (benign)	6–5–35, clear; attacks for three years, limited to dorsum of hands and one eyelid; cleared on intravenous injection of mercurochrome 220; Pels' test 60 per cent.

TABLE 2—*Concluded*

CASE	DATE ON WHICH SERUM WAS RECEIVED	PHYSICIAN'S CLINICAL IMPRESSION WHEN BLOOD WAS DRAWN	FINAL DIAGNOSIS
Group F. Serums obtained in cases in which a tentative clinical diagnosis of dermatitis herpetiformis was entertained, but which produced negative tests with dermatitis herpetiformis antigen.			
191			Neurodermatitis
211			Hodgkin's disease with bullae
357			Summer prurigo
379			Infectious eczematoid dermatitis
452			Infectious eczematoid dermatitis
472			Atopic eczema

Group G. Serums obtained in diseases distinct from dermatitis herpetiformis and from normal persons, and which produced negative tests with dermatitis herpetiformis antigen.

Herpes zoster	9	Cold allergy	1	Idiopathic exfoliative dermatitis	1
Recurrent herpes	4	Erythema nodosum	1	Ulcer of foot (etiology undetermined)	1
Pityriasis rosea	5	Eczema of hands	1	Malignant erythroderma	1
Herpes facialis	2	Contact dermatitis	1	Dermatitis exfoliativa venenata	1
Discoid lupus erythematosus	9	Scleroderma	4	Rosacea-like tuberculid (Lewandowsky)	1
Dermatitis medicamentosa	9	Bullous impetigo	1	Pemphigus	58
Lichen planus	4	Sprue	1	Lupus erythematosus (two recovered)	22
Infantile eczema	3	Thrush	1	Erythema multiforme	34
Infectious eczematoid dermatitis	1	Beriberi	1	Cases in which clinical diagnosis was not definitely established, but in which pemphigus was suspected	13
Pyoderma gangrenosum	1	Sarcoid	1		
Pellagra	2	Acne rosacea	2		
Angioneurotic edema	1	Aphthous stomatitis	2		
Atopic eczema	17	Vincent's angina	1		
Varicella	4	Vesicular toxic erythema (etiology undetermined)	1		
Urticaria	2	Recurrent vesicular eruption of mouth and penis (etiology undetermined)	1		
Ulcers of mouth (food sensitivity)	1	Normal persons	8		
Trichophytosis with trichophytid	3				
Lymphatic leukemia	1				

diagnosis of dermatitis herpetiformis was entertained, but in which it eventually was shown that the patients were suffering from diseases totally unrelated to dermatitis herpetiformis. All of these serums produced negative tests with dermatitis herpetiformis antigen and control antigens.

Group G consists of a control group of serums obtained from 238 patients who were well or who had cutaneous or systemic diseases definitely distinct from dermatitis herpetiformis. A negative test with the dermatitis herpetiformis antigen was obtained with each of these serums.

It is apparent that positive tests with dermatitis herpetiformis antigen were

obtained with the serums in seventy-five cases, in fifty-five of which (group A) an undisputed clinical diagnosis of dermatitis herpetiformis was made, in five of which (group B) a clinical diagnosis of herpes gestationes was made, in twelve of which (group C) a probable but as yet not definitely established clinical diagnosis of dermatitis herpetiformis was made, and in three of which (group E) a clinical diagnosis other than dermatitis herpetiformis was made. Negative tests with the dermatitis herpetiformis antigen were obtained with the serums in 247 patients. In three of these cases (group D) a clinical diagnosis of dermatitis herpetiformis was favored but a positive test with the pemphigus antigen was obtained in each instance. In six cases (group F) dermatitis herpetiformis was suspected clinically but was later ruled out. In 238 cases (group G) the clinical diagnosis was definitely not dermatitis herpetiformis but any one of various other cutaneous and systemic diseases.

Analysis and consideration of the results of this test as applied to lupus erythematosus

Table 3 shows the results of this test, together with the available clinical data, as it has been applied as a diagnostic test for lupus erythematosus. Group A consists of the serums from twenty patients in whom the clinical diagnosis of disseminate lupus erythematosus is definitely established. A positive test with lupus erythematosus antigen was obtained with the serum from each of these patients. In one patient (138) the clinical picture at the time the serum was drawn was that of the Senear-Usher type of pemphigus.

Group B consists of the serum from a patient in whom the clinical diagnosis at the time the serum was drawn was Senear-Usher type of pemphigus. As is noted in the table, this patient subsequently died of a hemolytic streptococcic septicemia. The cutaneous picture at the time of death was that of pemphigus vulgaris. This serum gave a positive test with the lupus erythematosus antigen and negative tests with the control antigens. In this case the question of a pemphigoid type of lupus erythematosus is raised.

Group C includes the serums which were obtained from two patients who had recovered from subacute disseminate lupus erythematosus. In case 286 the serum was drawn three years after recovery and in case 450 it was drawn four years after recovery. Both of these serums produced negative tests with the lupus erythematosus antigen and control antigens. Apparently, in the event of complete recovery, the antibodies responsible for the reduction of the mobility of the specific streptococci are lost.

Group D includes the serums obtained in eleven cases in which a tentative clinical diagnosis of disseminate lupus erythematosus was entertained. It was eventually shown that six of these patients were suffering from diseases wholly unrelated to lupus erythematosus and that five had the discoid type of lupus erythematosus. All of these serums produced negative tests with the lupus erythematosus antigen and control antigens. At half dilution there was a slight reduction of the mobility of the streptococci comprising the lupus erythematosus antigen by some of the serums of patients who had lupus erythematosus discoides.

TABLE 3

Results of the diagnostic test for lupus erythematosus

CASE	DATE ON WHICH SERUM WAS RECEIVED	PHYSICIAN'S CLINICAL IMPRESSION WHEN BLOOD WAS DRAWN	SUBSEQUENT COURSE
Group A. Serums which were obtained in cases in which a clinical diagnosis of disseminate lupus erythematosus was established, and which produced positive tests with lupus erythematosus antigen.			
68	8–10–33	Subacute disseminate lupus erythematosus	11–21–35, lesions of face and scalp
72	9–12–33	Subacute disseminate lupus erythematosus	8–24–35, health good; lesions around mouth
77	9–19–33	Subacute disseminate lupus erythematosus	Died 9–17–34, autopsy; lupus erythematosus, bronchopneumonia, glomerulonephritis and pericarditis; 9–28–33 serum positive with lupus erythematosus antigen
87	10– 5–33	Acute disseminate lupus erythematosus	Died of acute lupus erythematosus
133	4– 2–34	Disseminate lupus erythematosus	8–14–35, treated for lupus erythematosus; improved.
138	4–11–34	Senear-Usher syndrome	6–3–35, clinically lupus erythematosus
168	6–22–34	None given	2–29–36, subacute lupus erythematosus; good condition; pigmentation and alopecia
179	7–16–34	Subacute disseminate lupus erythematosus	10–28–34, skin lesions; clinically typical subacute lupus erythematosus
197	8– 3–34	Subacute disseminate lupus erythematosus	8–5–35, no active lesions; foci removed; on quinine.
198	8– 6–34	Disseminate lupus erythematosus	10–15–35, treated for lupus erythematosus; improved, leukopenia
208	8–20–34	Subacute disseminate lupus erythematosus	6–15–35, improving on gold; typical lupus erythematosus.
228	9– 7–34	Subacute disseminate lupus erythematosus	1–13–36, improved; typical lupus erythematosus.
282	2–20–35	Subacute disseminate lupus erythematosus	4–11–36, improved; relapsed March, 1936. Typical lupus erythematosus disseminate.
367	7–26–35	Subacute disseminate lupus erythematosus	3–3–36, improved; typical lupus erythematosus.
369	7–27–35	Subacute disseminate lupus erythematosus	Typical subacute lupus erythematosus. Last seen 9–20–35.
375	8–12–35	Acute disseminate lupus erythematosus	1–10–36, quite ill with lupus erythematosus
381	8–21–35	Acute disseminate lupus erythematosus	Died 11–6–35, of acute lupus erythematosus
436	11–19–35	Subacute disseminate lupus erythematosus	6–20–36, in hospital; generalization after gold; biopsy typical subacute disseminate lupus erythematosus

TABLE 3—*Continued*

CASE	DATE ON WHICH SERUM WAS RECEIVED	PHYSICIAN'S CLINICAL IMPRESSION WHEN BLOOD WAS DRAWN	SUBSEQUENT COURSE
		Group A—*Continued*	
437	11–19–35	Subacute disseminate lupus erythematosus.	1–9–36, bedfast; quite ill with lupus erythematosus
487	5–13–36	Acute disseminate lupus erythematosus	5–23–36, died of acute disseminate lupus erythematosus
		Group B. Serum which was obtained in a case in which the clinical diagnosis was Senear-Usher syndrome, but which produced a positive test with lupus erythematosus antigen.	
183	7–23–34	Senear-Usher syndrome	4–21–36, died; positive blood culture for hemolytic streptococci, antemortem; necropsy—chronic fibrous pleuritis, fatty vacuolization of liver and pyelonephritis; skin clinically pemphigus
		Group C. Serums which were obtained in two cases in which the patients recovered from definite lupus erythematosus disseminatus, but which produced negative tests with the lupus erythematosus antigen.	
286	3– 5–35	Subacute disseminate lupus erythematosus	1930, subacute disseminate lupus erythematosus; confirmed by biopsy; recovered; clear for three years.
450	1–29–36	Subacute disseminate lupus erythematosus	4–19–32, typical acute disseminate lupus erythematosus; biopsy quite typical; recovered; clear for three years.
		Group D. Serums which were obtained in cases in which a tentative clinical diagnosis of disseminate lupus erythematosus was entertained, but which produced negative tests with the lupus erythematosus antigen.	
			FINAL DIAGNOSIS
8			Sarcoids
78			Atopic eczema
130			Acne Rosacea
148			Acne rosacea
185			Discoid lupus erythematosus
209			Discoid lupus erythematosus
210			Discoid lupus erythematosus
337			Discoid lupus erythematosus
395			Discoid lupus erythematosus
466			Rosacea-like tuberculid of Lewandowsky
467			Henoch's purpura

TABLE 3—*Concluded*

Group E. Serums which were obtained in diseases unrelated to disseminate lupus erythematosus, discoid lupus erythematosus, and from normal persons, and which produced negative tests with lupus erythematosus antigen.

Herpes zoster	9	Varicella	4	Lymphatic leukemia	1
Recurrent herpes	4	Urticaria	2	Ulcer of foot—(etiology undetermined)	1
Pityriasis rosea	5	Cold allergy	1	Idiopathic exfoliative dermatitis	1
Herpes facialis	2	Erythema nodosum	1	Bullous impetigo	1
Discoid lupus erythematosus	4	Eczema of hands	1	Vincent's angina	1
Dermatitis medicamentosa	9	Contact dermatitis	2	Pemphigus	58
Lichen planus	4	Schleroderma	4	Dermatitis herpetiformis	55
Infantile eczema	3	Neurodermatitis	1	Herpes gestationes	5
Infectious eczematoid dermatitis	3	Hodgkin's disease	1	Erythema multiforme	34
Pyoderma gangrenosum	1	Summer prurigo	1	Normal persons	8
Pellagra	2	Trichophytosis with trichophytid	3	Cases in which clinical diagnosis was not yet definitely established. (Pemphigus was suspected in 15 and dermatitis herpetiformis in 15)	30
Angioneurotic edema	1	Ulcers of the mouth; food sensitivity	1		
Atopic eczema	16	Aphthous stomatitis	2		
Recurrent vesicular lesions of mouth and penis (etiology undetermined)	1	Beriberi	1		
Malignant erythroderma	1	Dermatitis exfoliativa (venenata)	1		
		Thrush	1		
		Sprue	1		

Group E consists of a control group of serums of 288 patients, 284 of whom were well or had cutaneous or systemic diseases definitely distinct from disseminate lupus erythematosus and four of whom had the chronic discoid type of lupus erythematosus. A negative test with the lupus erythematosus antigen was obtained with each of these serums.

It is evident that positive tests with the lupus erythematosus antigen were obtained with the serums obtained in twenty-one cases. In twenty cases (group A) a definite clinical diagnosis of disseminate lupus erythematosus was established, and in one case (group B) a clinical diagnosis of pemphigus was made. Negative tests with the lupus erythematosus antigen were obtained with the serums in 301 cases. In two of these (group C) the serums were drawn from patients who had recovered from subacute disseminate lupus erythematosus three and four years respectively before the test was performed. In eleven cases (group D) disseminate lupus erythematosus was suspected clinically but was later ruled out. In the remaining 288 cases (group E) the clinical diagnosis was definitely not disseminate lupus erythematosus but any of various other cutaneous and systemic diseases. Groups D and E comprise the serums from five patients and four patients respectively who had the chronic discoid type of lupus erythematosus. Very weakly positive tests with the lupus erythematosus antigen were obtained with five of these nine serums, but only when they were tested at half the usual dilution of serum. From these results it must be con-

TABLE 4

Results of the diagnosis test for erythema multiforme

CASE	DATE ON WHICH SERUM WAS RECEIVED	PHYSICIAN'S CLINICAL IMPRESSION WHEN BLOOD WAS DRAWN	SUBSEQUENT COURSE
Group A. Serums which were obtained in cases in which a clinical diagnosis of erythema multiforme exudativum was established, and which produced positive tests with erythema multiforme antigen.			
47	6–12–33	Erythema multiforme	6–13–35, no recurrence; clinically erythema multiforme.
63	7–27–33	Bullous erythema multiforme	3–24–36, clinically erythema multiforme; no recurrence.
66	8–4–33	Erythema multiforme	8–2–34, recurrence, typical erythema multiforme; Pels' test 75 per cent—non-toxic; 8–2–34, serum positive with erythema multiforme antigen.
111	2–13–34	Erythema multiforme	7–3–35, not seen recently; clinically erythema multiforme.
121	2–20–34	Erythema multiforme	6–2–36, typical erythema multiforme; no recurrence.
135	4–6–34	Erythema multiforme	6–15–35, typical course of erythema multiforme.
140	4–12–34	Erythema multiforme	6–5–35, not seen recently; clinically erythema multiforme.
143	4–18–34	Erythema multiforme	June, 1935, recurrence followed extraction of teeth; well then.
145	4–18–34	Pemphigus	3–27–36, ran course of erythema multiforme; no recurrence; 8–2–35, serum negative with all antigens.
162	5–31–34	Erythema multiforme	6–5–35, had typical erythema multiforme.
188	7–19–34	Erythema multiforme or pemphigus	October, 1935, typical course of erythema multiforme; well then.
194	7–31–34	Herpes gestationes or erythema multiforme	6–19–36, recurrence, again pregnant; began during pregnancy; fifth attack; Pels' test 53 per cent—toxic.
225	9–1–34	Erythema multiforme	4–6–36, typical bullous erythema multiforme; no recurrence
244	10–19–34	Erythema multiforme	3–28–36, typical erythema multiforme; several attacks.
251	11–21–34	Erythema multiforme and recurrent herpes	4–9–36, cyclic recurrences of erythema multiforme preceded by recurrent herpes of buttocks; 4–9–36, serum positive with erythema multiforme antigen.
254	12–10–34	Erythema multiforme	5–15–35, no recurrence; spring and fall attacks 6 years.
261	12–27–34	Erythema multiforme or pemphigus	4–14–36, favored erythema multiforme; not seen recently.
263	1–3–35	Erythema multiforme	October, 1935, no recurrences; typical erythema multiforme
267	1–12–35	Erythema multiforme or dermatitis medicamentosa	4–4–36, had recurrences; no reaction to drugs
270	1–17–35	Erythema multiforme	3–21–36, ten attacks, typical erythema multiforme.

TABLE 4—*Continued*

CASE	DATE ON WHICH SERUM WAS RECEIVED	PHYSICIAN'S CLINICAL IMPRESSION WHEN BLOOD WAS DRAWN	SUBSEQUENT COURSE
		Group A—*Continued*	
277	2-4-35	Erythema multiforme	3-21-36, recurrence; spring and fall attacks for six years.
283	2-20-35	Erythema multiforme	3-21-36, typical erythema multiforme; several previous attacks.
290	3-11-35	Erythema multiforme	4-20-36, typical attack of erythema multiforme; 4-16-36, serum positive with erythema multiforme antigen.
293	3-18-35	Erythema multiforme	3-24-36, having recurrences; typical erythema multiforme
294	3-18-35	Erythema multiforme	3-9-36, recurrence; attacks for three years typical erythema multiforme.
299	5-10-36	Erythema multiforme	4-1-36, typical erythema multiforme; recurrent type.
338	5-2-35	Erythema multiforme	October, 1935, recurrence; typical erythema multiforme.
355	6-18-35	Erythema multiforme	4-3-35, one recurrence; attacks spring and fall for three years.
365	7-23-35	Erythema multiforme	3-31-36, typical bullous erythema multiforme; 1-4 attacks a year for eight years.
370	8-1-35	Erythema multiforme	3-12-36, recurrence in mouth; many recurrent attacks before test; clinically erythema multiforme.
440	12-2-35	Erythema multiforme	6-2-36, typical erythema multiforme; well then.
449	1-8-36	Erythema multiforme	6-2-36, typical erythema multiforme; well then.
461	3-19-36	Erythema multiforme	5-25-36, clear; was typical erythema multiforme; spring and fall attacks for eight years.
484	4-20-36	Erythema multiforme	Spring and fall attacks for four years; typical erythema multiforme.

Group B. Serums which were obtained in cases in which a tentative diagnosis of erythema multiforme was entertained but which produced negative tests with the erythema multiforme antigen.

			FINAL DIAGNOSIS
129			Trichophytosis with bullous trichophytid
224			Dermatitis medicamentosa (phenolphthalein)
237			Ulcerations of mouth—food sensitivity
252			Trichophytosis with trichophytid of the erythema multiforme type
255			Dermatitis medicamentosa
301			Iododerma
333			Aphthous stomatitis
451			Dermatitis medicamentosa (veronal)
464			Trichophytosis with trichophytid

TABLE 4—*Concluded*

Group C. Serums which were obtained in diseases distinct from erythema multiforme and from normal persons, and which produced negative tests with the erythema multiforme antigen.

Herpes zoster	9	Eczema of hands	1	Recurrent vesicular lesions of mouth and penis (etiology undetermined)	1
Recurrent herpes	4	Contact dermatitis	2		
Pityriasis rosea	5	Scleroderma	4		
Herpes facialis	2	Sarcoid	1	Dermatitis exfoliative (venenata)	1
Discoid lupus erythematosus	9	Acne Rosacea	2		
		Neurodermatitis	1	Ulcer of foot (etiology undetermined)	1
Dermatitis medicamentosa	5	Hodgkin's disease	1		
		Summer prurigo	1	Idiopathic exfoliative dermatitis	1
Lichen planus	4	Aphthous stomatitis	1		
Infantile eczema	3	Beriberi	1	Pemphigus	58
Infectious eczematoid dermatitis	3	Malignant erythroderma	1	Dermatitis herpetiformis	55
Pyoderma gangrenosum	1	Thrush	1		
Pellagra	2	Lymphatic leukemia	1	Lupus erythematosus (two recovered)	22
Angioneurotic edema	1	Sprue	1		
Atopic eczema	17	Bullous impetigo	1	Cases in which clinical diagnosis was not yet definitely established (In sixteen cases pemphigus was suspected and in fifteen cases dermatitis herpetiformis was suspected.)	31
Varicella	4	Vincent's angina	1		
Urticaria	2	Rosacea-like tuberculid of Lewandowsky	1		
Cold allergy	1				
Herpes gestationes	5				
Normal persons	8	Vesicular toxic erythema—etiology undetermined	1		
Erythema nodosum	1				

cluded that the serums of patients who have chronic discoid lupus erythematosus do not contain antibodies of the type demonstrable by this test (as usually run) for the specific streptococcus isolated from patients who have lupus erythematosus disseminatus or at least they do not contain them in sufficient titer to admit of detection by this method in its present state of sensitiveness. This may be interpreted as evidence that these two types of lupus erythematosus do not have a common etiologic agent. However, this point needs further investigation, since there is a very slight reaction at low dilutions of serum.

Analysis and consideration of the results of this test as applied to erythema multiforme

In table 4 are recorded the results of this test, together with the available clinical data, as it has been applied to erythema multiforme. Group A consists of the serums obtained in thirty-four cases in which a definite clinical diagnosis of erythema multiforme is established. A positive test was obtained with the erythema multiforme antigen and the serum of each of these patients.

Group B consists of the serums obtained from nine cases in which the clinical findings were those of erythema multiforme at the time the serum was drawn. At this time a tentative diagnosis of erythema multiforme was considered. Subsequently, these patients were all shown to be suffering from diseases with established etiologic agents that distinguished them from the infectious type of

erythema multiforme. The serum of each of these patients produced a negative test with erythema multiforme antigen and control antigens. It is an accepted fact that the clinical picture of erythema multiforme may be produced by many varied infectious and noninfectious agents. By the application of this test to the serums of patients presenting the clinical findings of erythema multiforme, it has thus been possible to distinguish between the so-called idiopathic or vernal type of erythema multiforme and the erythema multiforme-like eruptions due to sensitization to foods and drugs or those caused by other types of infections, such as fungus infection.

Group C includes control serums obtained from 279 patients who were well or who had cutaneous or systemic diseases distinct from erythema multiforme. Some of the patients in this group had eruptions resembling erythema multiforme. All of these serums produced negative tests with the erythema multiforme antigen.

Positive tests were obtained with the serums in thirty-four cases (group A) in which a definite clinical diagnosis of erythema multiforme was established. Negative tests with the erythema multiforme antigen were obtained with the serums in 288 patients. In nine of these cases (group B) eruptions which had the morphology of erythema multiforme were present at the time the serums were drawn. These eruptions were later found to be due to various causes, which distinguished them from true erythema multiforme exudativum. In the other 279 cases (group C) the serums were taken from patients who had cutaneous or systemic diseases definitely distinct from erythema multiforme, and from well persons.

COMMENT

It has been shown that the specific reduction of the cataphoretic mobility of an organism that results from treatment of that organism with a serum, is the result of the presence in that serum of antibodies specific for that organism (10, 11, 12, 13, 14, 15 16). Therefore, the results of these tests may be interpreted as indicative of the specificity of the respective streptococci isolated from patients who had (1) pemphigus, (2) dermatitis herpetiformis, (3) lupus erythematosus disseminatus, and (4) erythema multiforme exudativum. Hence, this report of the results of these tests is made at this time to add support to the previously presented evidence of the specificity of the respective streptococci isolated from patients who had the four diseases named (1–5).

The use of this procedure as a differential diagnostic test for these four diseases is at present impractical for wide application. This statement is based on the fact that there are certain unstable influencing factors which still want of adequate control. One of the greatest sources of difficulty in this regard is that, in spite of all efforts to date, the antigens gradually deteriorate. Therefore, it is necessary to have a constant source of fresh material from which new antigens can be regularly obtained so that in a particular "set-up," antigens of approximately the same age may be used. Many advances in stabilization of these antigens have been made and efforts directed toward this end will be continued.

Another fact which has been responsible for a great amount of difficulty is that fresh serums in most instances give unsatisfactory tests. Such serums usually reduced equally to a slight or moderate degree the mobility of each of the four antigens used and failed to show a specific marked action on the specific antigen. In the case of most serums, after aging in the refrigerator for from seven to ten days, this apparently inhibiting mechanism on the specific antibody disappeared and tests performed after that time demonstrated the usual marked reduction of the mobility of the specific antigen. Investigations have been started and will be continued in an effort to establish a method of producing this effect of aging in serums rapidly. Until methods of control of these and of other as yet unstable features of this delicate test are worked out, it cannot be widely applied. Long training in the reading of the test is necessary and a great personal factor exists in this respect. It is to be hoped that investigations which have already been started will lead to methods of control of the unstable influencing factors to such a degree that this test can be adapted to wide usage.

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